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Characterization of primary female infertility in a Nigerian tertiary hospital: A case-control study

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Izuchukwu A. Okafor[*1,2,4] *Oluseun O. Saanu*[3], *Oladapo Olayemi*[1,2,3] *and Akinyinka O. Omigbodun*[1,2,3]

Reproductive Health Science Program, Pan African University of Life and Earth Science Institute (Including Health and Agriculture), PAULESI, University of Ibadan, Ibadan, Nigeria[1]; Department of Obstetrics and Gynaecology, Faculty of Clinical Sciences, College of Medicine, University of Ibadan, Ibadan[2]; Department of Obstetrics and Gynaecology, University College Hospital, Ibadan, Nigeria[3]; Department of Anatomy, Faculty of Basic Medical Sciences, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, Nnewi, Nigeria[4]

***For Correspondence**: Email: *okaforizuchukwu33@gmail.com*; Phone: +2348030716546

Abstract

Primary female infertility is a serious reproductive health concern amongst many women in Nigeria with associated psychosocial impact. There is a need for early prediction of this disorder for increased chances of fertility in Nigerian women. This study reported the anthropometric, sociodemographic, and clinical baseline characteristics of primary infertility females and studied their viability as predictors of primary infertility. This is a case-control study of primarily infertile (54) and fertile (50) Nigerian females aged 20-44 years recruited by random selection of patients who visited University College Hospital between August and November 2020. A clinical proforma was utilized to assess sociodemographic data, fertility history and clinical diagnosis of study participants. The body mass index (BMI) of both fertile and infertile females was in the overweight category (27.98±0.87 and 28.18±0.59, respectively). Both fertile and primary infertile females present a normal menarcheal age (13.68±0.27 and 13.91 ± 0.32 years, respectively), and there was no significant difference between the menarcheal age (p = 0.411) in both study groups. Ovarian disorder was the most contributing clinical diagnosis (67%) of primary infertility. There is a significant strong association between menarcheal age, ovarian factor infertility ($\chi 2 = 13.839$, $\varphi_c = 0.458$, p = 0.008) and tubal factor infertility ($\chi 2 = 11.111$; $\varphi_c = 0.527$, p=0.025). Females with primary infertility may present with overweight in no significantly different way than fertile females and BMI may not be useful in predicting primary infertility. However, menarcheal age may be a valuable tool to predict the ovarian and tubal factors in primary infertility. *(Afr J Reprod Health 2022; 26[8]: 66-82).*

Keywords: Primary female infertility, fertility profile, menarcheal age, BMI, Nigeria

Résumé

L'infertilité féminine primaire est un grave problème de santé reproductive chez de nombreuses femmes au Nigeria, avec un impact psychosocial associé. Il est nécessaire de prévoir précocement ce trouble pour augmenter les chances de fertilité chez les femmes nigérianes. Cette étude a rapporté les caractéristiques anthropométriques, sociodémographiques et cliniques de base des femmes atteintes d'infertilité primaire et a étudié leur viabilité en tant que prédicteurs de l'infertilité primaire. Il s'agit d'une étude cas-témoins de femmes nigérianes primaires infertiles (54) et fertiles (50) âgées de 20 à 44 ans recrutées par sélection aléatoire de patients qui ont visité l'University College Hospital entre août et novembre 2020. Un formulaire clinique a été utilisé pour évaluer les données sociodémographiques. les données, les antécédents de fertilité et le diagnostic clinique des participants à l'étude. L'indice de masse corporelle (IMC) des femmes fertiles et infertiles se situait dans la catégorie du surpoids (27,98 ± 0,87 et 28,18 ± 0,59, respectivement). Les femmes fertiles et infertiles primaires présentent un âge normal de la ménarche (13,68 ± 0,27 et 13,91 ± 0,32 ans, respectivement), et il n'y avait pas de différence significative entre l'âge de la ménarche (p = 0,411) dans les deux groupes d'étude. Le trouble ovarien était le diagnostic clinique le plus contributif (67 %) de l'infertilité primaire. Il existe une forte association significative entre l'âge de la ménarche, l'infertilité ovarienne ($\chi 2 = 13,839$, $\varphi c = 0,458$, p = 0,008) et l'infertilité tubaire ($\chi 2 = 11,111$; $\varphi c = 0,527$, p=0,025). Les femmes atteintes d'infertilité primaire peuvent présenter un surpoids de manière non significativement différente des femmes fertiles et l'IMC peut ne pas être utile pour prédire l'infertilité primaire. Cependant, l'âge de la ménarche peut être un outil précieux pour prédire les facteurs ovariens et tubaires de l'infertilité primaire. *(Afr J Reprod Health 2022; 26[8]: 66-82).*

Mots-clés: Infertilité féminine primaire, profil de fécondité, âge de la ménarche, IMC, Nigéria

Introduction

Infertility, according to International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, is *a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse*[1]. Infertility is a critical part of reproductive health and contributes to one's total wellbeing. It makes an overt psychosocial impact in men and women, including depression, discrimination, and ostracism[2]. Infertility, a complex but common disease, is a worldwide problem affecting 8-12% of couples during their reproductive lives and demands a proper clinical examination of two sexual partners before a diagnosis can be established[3]. A ten-year systematic analysis had put the prevalence of infertility at 1.9% (an average of 48.5 million people), using a 5-year exposure period for couples. It had also shown that infertility has remained relatively constant between 1990 and 2010[4]. Sub-Saharan Africa has been reported to have one of the highest prevalence of primary (>3%) infertility in the world[4].

Venkatesh and colleagues defined female infertility as the inability to conceive naturally or to carry a pregnancy to full term[2] which accounts for about 37% of infertility cases among couples[5]. The International Glossary on Infertility and Fertility Care has defined female infertility as *infertility caused primarily by female factors encompassing: ovulatory disturbances; diminished ovarian reserve; anatomical, endocrine, genetic, functional, or immunological abnormalities of the reproductive system; chronic illness; and sexual conditions incompatible with coitus*[6]. The above-named female factors could lead to a primary or secondary form of female infertility. Primary female infertility occurs when *'a woman who has never been diagnosed with a clinical pregnancy and meets the criteria of being classified as having infertility'*[6].

Over the years, several studies have identified some causes of primary infertility (not being able to be pregnant after at least one year of having unprotected sex). Clinically, infertility is a highly heterogeneous pathology with a complex aetiology that includes environmental and genetic factors[7]. There is growing evidence that genetic abnormalities are present in as many as 10% of infertile females[8]. Infertility is broadly grouped based on its causative factors, including male, female, combined, or unexplained factors, and their prevalence varies across different populations[2].

To ensure evidence-based female fertility diagnosis, management and overall response, continuous monitoring and evaluation of disease prevalence, characteristics, and associated factors is sacrosanct[9]. In this present study, we have attempted to characterise primary female infertility using a tertiary clinical setting to determine the current trends and compare these to existing studies. It is important to note that we have characterised primary female infertility in a controlled study setting to detect distinguishing features of primary female infertility. This study observed several factors, including sociodemographics, lifestyle, clinical and family history. This present study is the first Nigerian case-control study to characterise primary female infertility in a tertiary clinical setting, with several factors observed. We have given more detailed description of some of the variables investigated within the method section of this report.

In particular, there is a dearth of research on menarcheal age in primarily infertile Nigerian women[10]. Also, there is a growing interest in the role of menarcheal age in female infertility, and calls have been made for more research in different settings to delineate the perceived impact process[10]. A recent study showed that late menarcheal age (≥15 years) is associated with the likelihood of infertility amongst southwestern Nigerian women[11]. This necessitated our focus on the menarcheal age as a major characteristics observed in this study.

A multicountry population study reported a positive correlation between menarche and fertility status[12]. More importantly, menarcheal age studies from large representative samples of the female population showed varying trends in Nigeria's southern and northern regions[13,14]. In Nigeria, the mean menarcheal age of women underwent a marked secular decline between 1922 and 2003 from a mean average of 15.02 to 13.78[14], which has remained stable to date[13,15]. These fluctuations in reproductive parameters amongst Nigerian females were attributed to changes in socio-cultural and economic factors within the period[14]. This explains the current study's investigation of sociodemographics as a distinguishing factor in

primary female infertility. As there becomes more variety and trends to infertility issues globally, there is a need for more studies to keep track of localised trends on infertility for better clinical management and research strategy.

This study highlights the clinical profile of females with primary infertility in a Nigerian tertiary hospital in comparison with fertile women, and investigates the relationship between primary female infertility and some selected sociodemographics and clinical history. The study outcome will be an important update that will be useful for the prevention, diagnosis, treatment and research in primary female infertility in Nigeria and similar settings.

Methods

Study plan, recruitment and data collection

This is a case-control study of primarily infertile (54) and fertile (50) Nigerian females aged 20-44 years who presented to the gynecology and family planning clinic of University College Hospital, Ibadan, Nigeria between August and November 2020, as part of a more extensive study on primary female infertility. The study participants were recruited consecutively by randomly selecting patients who visited the clinic and met the fertility and primary infertility criteria as defined by WHO[1]. Patients with a history of abortion, husband infertility, and foreign phylogeny were excluded from the infertility study group. The fertile females recruited were those who have had at least a live birth within the last year at the time of this study and had no foreign phylogeny. This study utilised a structured clinical proforma containing three sections: 1) sociodemographic, 2) anthropometric and fertility history, and 3) clinical diagnosis and infertility risk factors. The clinical proforma was developed in English Language, considering the questions needed to meet the research objectives. A pilot survey was done with a population of five participants, and modifications were made to the proforma following the outcome and the inputs of the study supervisors. A non-affiliated researcher reviewed the proforma and validated by pretesting to ensure accuracy and efficiency. The final proforma was tested for consistency using internal consistency (Cronbach's alpha of 0.7), test-retest reliability, and inter-rater reliability (Kappa statistic, K = 0.9) with the first 15 subjects before the recruitment. The component details of the proforma sections can be found in the proforma (see supplementary file 1). The proforma was administered to each participant by trained reproductive health experts with the full consent of the participants. The experts gave verbal translations (Igbo, Hausa and Yoruba) of the study proforma to the participants during the administration of the proforma. When needed during the proforma administration in to ensure well-informed participation and reduce bias due to the language barrier.

Description of variables

The information collected through the three-sectioned clinical proforma includes weight, height, and body mass index (BMI), age, smoking status, alcohol consumption, contraceptive use, family history of infertility, age at menarche, diagnosis of infectious and non-infectious diseases and cause of infertility. These independent variables were handled as proportions except for age, menarcheal age, and BMI, which were reported as both proportional and continuous variables. The sociodemographic characteristics of the study participants were assessed with age, marital status, educational status, religion, occupation and ethnicity while the anthropometry were observed using the body weight, height and BMI indices. The clinical diagnosis of infertility among the primary infertile women were assessed, including cervical factors, tubal factors, hormonal factors, uterine factors, ovarian factors and unexplained factors. Some fertility history were also taken from the study participants: menarcheal age, duration of infertility and family history of infertility. The risk factors of female infertility were also assessed using the participant's age, STDs, smoking, alcohol use and prevalence of diabetes among the participants.

Menarcheal age classification used in this study is according to Glueck *et al*.[16]: early menarche (≤10 years), normal menarche (11-15 years), and late menarche (≥16 years); while the BMI Classification used was based on the WHO[17] and Centres for Disease Control and Prevention (CDC)[18] classifications: underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9), obese (30-34.9), severely obese (35-39.9), morbidly obese (>40). The family history of infertility

collected from participants includes that of the mother, father, sister, brother, cousin, uncle, aunty or a known distant relation. The assessment of the contraceptive use among the cases and controls were dependent on the prior or current use of any kind of contraceptive. The infectious diseases assessed include Human immunodeficiency virus (HIV), Chlamydia, Syphilis, Gonorrhea, Herpes simplex virus (HSV), Tuberculosis (TB), Human Papilloma Virus (HPV) and Hepatitis, while non-infectious diseases include diabetes and hypertension. The study participants with primary infertility reported all their diagnosed clinical causes of infertility which were categorized as: tubal, cervical, hormonal, uterine, ovarian and unexplained factors.

Data analysis

All data were recorded in Microsoft excel, cleaned and then transferred to IBM Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 21.0 for analysis. Variables were screened for normality using the Shapiro-Wilk test before choosing the statistical test. Descriptive statistical analysis was performed for all data. Continuous variables were presented using the mean and standard error of the mean, while categorical data were presented as frequency and counts. Association and correlation studies were done using the Chi-square test and Cramer's V (for categorical variables), and Pearson correlation test (for continuous variable). Data were considered statistically significant at $p< 0.05$.

Results

Sociodemographic pattern and anthropometry of study participants

The primarily infertile females were comparably distributed within all the age categories (between 22 - 27%) except for the 20-24 year category that formed only 3.7% of the study group population. This is similar in the infertile group, but only 2% and 8% were observed in the 20-24 and 25-29 age groups, respectively. A little over 90 % of the infertile women were still married, while all the fertile females were married. About 15% of the infertile women did not have at least a secondary education compared to 24% in fertile women. The majority of the infertile women were Christians (70.4%), of the Yoruba ethnic group (75.9%) and self-employed (53.7%). This similar trend was observed in the infertile group - 68% (Christians) and 82% (Yorubas). Civil service (40%) and self-employment (40%) equally were the major occupation among the fertile females. The average BMI of both the cases (27.98±0.87) and controls (28.18±0.59) were in the overweight category. Only 35% of women with primary infertility have normal weight while others were either overweight (30%), obese (17%), severely obese (11%), or morbidly obese (6%), except for one participant (2%) who was underweight. However, only 26% of the fertile women had normal weight, while others were either overweight (38%) or obese (32%), with very few severely obese (4%) and none with morbid obesity (0%) (Table 1). No statistically significant difference was observed in this study for all the biodemographic parameters assessed in fertile and infertile women ($p>0.05$).

History and clinical characteristics of study participants

The range of infertility duration for the infertile females is 1-20 years with a median duration of 5 years (CI: 4.18 - 7.88), compared to the control with a median of 8.50 for marriage duration with a range of 1-25. These results were not compared since they were dissimilar. Our results showed a higher menarcheal age in the infertile group (13.91 ± 0.32 years) than the fertile women (13.68±0.27). However, both remain in the normal menarcheal age range, and the difference was not statistically significant ($p=0.411$). However, about 2% and 17% were observed to have had either early or late menarche, respectively in the infertile group compared to the fertile group presenting no female who experienced early menarche and a few (16%) that had late menarche. None of the study participants have ever smoked, and a majority of them do not consume alcohol (83% for cases and 87.8% for controls). While about 91% of the infertile women have never made use of contraceptives before (91%), the infertile group had either used for less than five years (28%) or more (10%). There was a family history of infertility in both the infertile female group (13%) and the fertile females (28%), with an insignificant difference between the groups ($p=0.153$). There was a low prevalence of both infectious (HIV: 3%; HSV: 3%; Syphilis: 2%; Chlamydia: 5%; Hepatitis: 3%; TB: 3%) and non-infectious disease (diabetes: 5%;

Table 1: Biodemographic indices of study participants

Parameters	Categories	Primary infertile females (n=54)	Fertile females (n=50)	P-value
Age category (years)	20-24	2 (3.7)	1 (2)	0.629
	25-29	15 (27.8)	4 (8)	
	30-34	12 (22.2)	18 (36)	
	35-39	13 (24.1)	13 (26)	
	40-44	12 (22.2)	14 (28)	
Marital status	Single (never married)	4 (7.4)	0 (0)	NE
	Married	49 (90.7)	50 (100)	
	Divorced*	1 (1.9)	0 (0)	
Education[@]	Primary	2 (3.7)	2 (4)	0.901
	Secondary	6 (11.1)	10 (20)	
	Undergraduate/graduate	31 (57.4)	24 (48)	
	Postgraduate	15 (27.8)	14 (28)	
Religion[@]	Christian	38 (70.4)	34 (68)	0.746
	Islam	16 (29.6)	16 (32)	
Occupation	Unemployed/housewife	4 (7.4)	3 (6)	0.569
	Student	4 (7.4)	0 (0)	
	Self employed/business	29 (53.7)	20 (40)	
	Corporate work	3 (5.6)	4 (8)	
	Civil servant	10 (18.5)	20 (40)	
	Others	4 (7.4)	3 (6)	
Ethnicity	Igbo	2 (3.7)	4 (8)	0.637
	Hausa	3 (3.56)	0 (0)	
	Yoruba	41 (75.9)	41 (82)	
	Others[$]	8 (14.8)	5 (10)	
Biometry[β]	Height (m^2)	1.58±0.01	1.57±0.01	0.359
	Weight (kg)	69.48±1.97	69.56±1.90	0.97
	BMI (Kg/m^2)	27.98±0.87	28.18±0.59	0.848
Weight status (by BMI classification)[¥]	Underweight	1 (2)	0 (0)	0.325
	Normal weight	19 (35)	13 (26)	
	Overweight	16 (30)	19 (38)	
	Obese	9 (17)	16 (32)	
	Severely obese	6 (11)	2 (4)	
	morbidly obese	3 (6)	0 (0)	

Data were expressed as frequencies and percentages (in brackets). BMI: Body mass index. [@]Categories with zero frequency were not shown. [¥]Weight status follows WHO and CDC classification. [*]Divorced females must have remained in regular sex in the last one year intending to conceive. [$]Includes Edo, Urhobo, Igede, Ibibio, Youm and Akwaibom ethnic groups. [β]values were given as mean±standard error of the mean. NE: not evaluated in SPSS due to zero value in one of the study groups. The significance level was set at $p<0.05$.

hypertension: 10%) within the infertile study population. There was also a low prevalence of hypertension (13.8%) and diabetes (3.8) in the fertile female group with only HIV (10.3%) as the infectious disease reported. The difference between the non-infectious disease in the fertile and infertile groups was not significant ($p>0.05$) (Table 2). Of all the history and clinical characteristics of the study participants assessed, only the use of contraceptives was significantly different in the fertile and infertile female groups ($p<0.001$). Table 3 shows the relationship between menarcheal age, BMI, and infertility duration in fertile and infertile females. There was no significant correlation between menarcheal age, BMI, and infertility duration in both study populations ($p>0.05$). Figure 1 shows the trend analysis and comparison of primary infertility duration between the menarcheal age groups of primary infertile women. The increased infertility duration observed in females with early and late menarche was not statistically significant ($p=0.163$), with homogenous variances between the groups ($p=0.178$). Also, the increased BMI seen in females with normal menarche and lower BMI in late menarche across fertile and infertile females was not statistically significant ($p=0.283$ and 0.224 respectively) with an observation of homogenous variances between the

Table 2: History and clinical characteristics of study participants

Parameters	Categories	Primary infertile females (n=54)	Fertile females (n=50)	P-value
Duration of infertility/marriage duration (years)*		Median = 5; Range = 1-20 (CI: 4.18 – 7.88); IR = 7	Median = 8.50; Range = 1-25 (CI: 6.94 – 9.94); IR = 6.50	NC
Menarcheal age [β] (years)		13.90 ± 0.25	13.68±0.27	0.411
Menarche classification[¥]	Early	2 (3)	0 (0)	
	Normal	43 (80)	42 (84)	0.722
	Late	9 (17)	8 (16)	
Alcohol consumption[@]	Not at all	45 (83)	43 (87.8)	
	<1yr	3 (6)	5 (10.2)	
	1-5yrs	2 (4)	0 (0)	0.250
	Stopped taking	4 (7)	1 (2)	
Use of Contraceptives[@]	Never	49 (91)	26 (52)	
	0-5 yrs	5 (9)	14 (28)	
	>5 yrs	0 (0)	5 (10)	**<0.001**
	Not in use now	0 (0)	5 (10)	
Family history of infertility	Yes	7 (13) [$]	14 (28) [$]	
	No	44 (81)	33 (66)	0.153
	Don't know	3 (6)	3 (6)	
Non-infectious diseases[#]	Diabetes	2 (5)	1 (3.8)	>0.99
	Hypertension	4 (10)	4 (13.8)	0.712
STDs/STIs[#€]	HIV	1 (3)	3 (10.3)	0.302
	HSV	1 (3)	0 (0)	NE
	Syphilis	1 (2)	0 (0)	NE
	Chlamydia	2 (5)	0 (0)	NE
	Hepatitis	1 (3)	0 (0)	NE
	Tuberculosis	1 (3)	0 (0)	NE
Infertility diagnosis	Ovarian disorder (n=33)	22 (67)	NO	
	Tubal disorders (n=20)	9 (45)	NO	
	Cervical disorders (n=19)	6 (32)	NO	
	Uterine disorders (n=23)	12 (52)	NO	
	Hormonal disorders (n=26)	16 (62)	NO	
	Unexplained factors (n=19)	11 (58)	NO	

Data were expressed as frequencies and percentages (in brackets). [@]Categories with zero frequency were not shown. [¥]Menarcheal age classification is according to Glueck *et al*. (2013). Data was not normally distributed as shown by both Shapiro Wilk and Kolmogorov Smirnov tests; n=49 (cases) and 50 (control); Duration of infertility was assessed for cases while marriage duration was assessed for the non-cases. [#]sample size for each category ranges from 39 to 41 due to attrition. [$]The participants had multiple family histories of infertility (cases: father – 1/7; mother – 6/7; brother – 1/7; sister – 3/7; cousin – 1/7 and non-cases: father – 1/14; mother – 2/14; aunt – 1/14; sister – 4/14; uncle – 2/14; distant relation: 4/14). [β]values were given as mean±standard error of the mean. [€]Gonorrhea and HPV were assessed but not included due to zero value; one participant reported 'other' infectious disease, which was not specified. The smoking status of participants was assessed but not included because it had a zero value. NE: not evaluated in SPSS due to zero value in one of the study groups. NO: Not observed in the study group. NC: Not comparable due to dissimilar data. The significance level was set at $p<0.05$.

groups (p=0.075 and 0.839 respectively) (Figure 2).

Clinical diagnosis of primary female infertility

Table 2 shows the distribution of the clinical diagnosis of primary infertility amongst the infertile female participants. Ovarian disorders were the most contributing clinical diagnosis (67%) of primary infertility in our study cohort, followed by hormonal factors (62%), while cervical factors were the least (32%). More than half of the respondents (58%) reported their infertility clinical diagnosis as unexplained. Table 4 shows the association between the clinical diagnosis of primary infertility, participant's age, menarcheal age, and BMI categories. There was no significant association between the BMI categories and any clinical diagnoses of infertility ($p>0.05$). There was a strong significant association between menarcheal age,

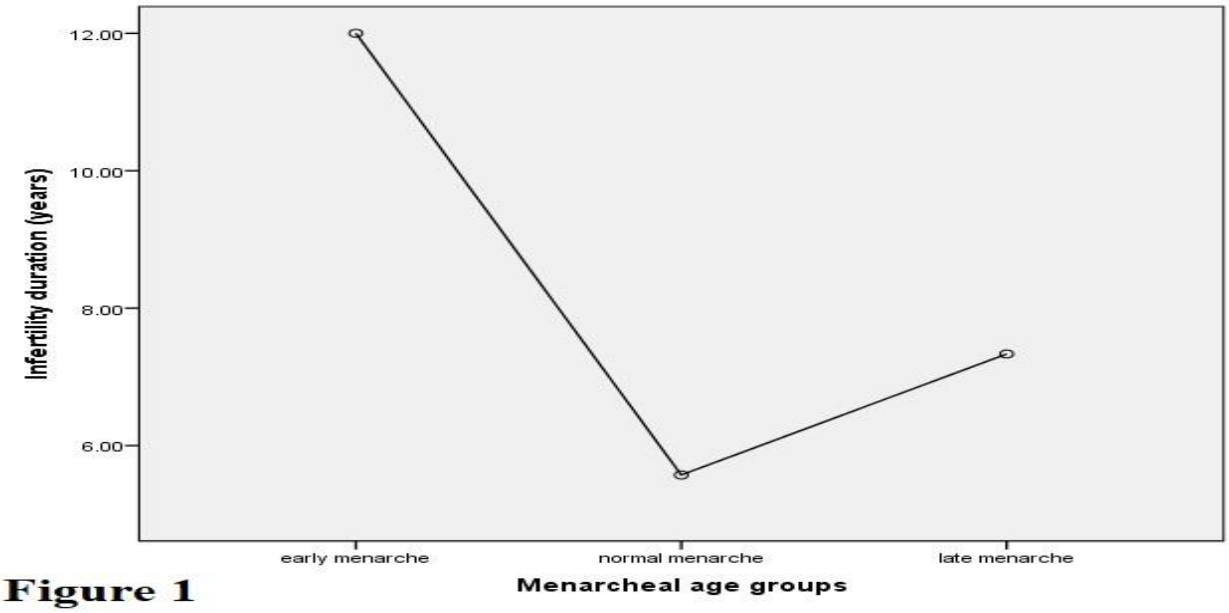

Figure 1: Trend analysis and comparison of infertility duration between the Menarcheal age groups of primary infertile women. The mean values of the infertility duration (in years) were presented. Comparison between the infertility duration seen across menarcheal age groups were considered significant at $p<0.05$.

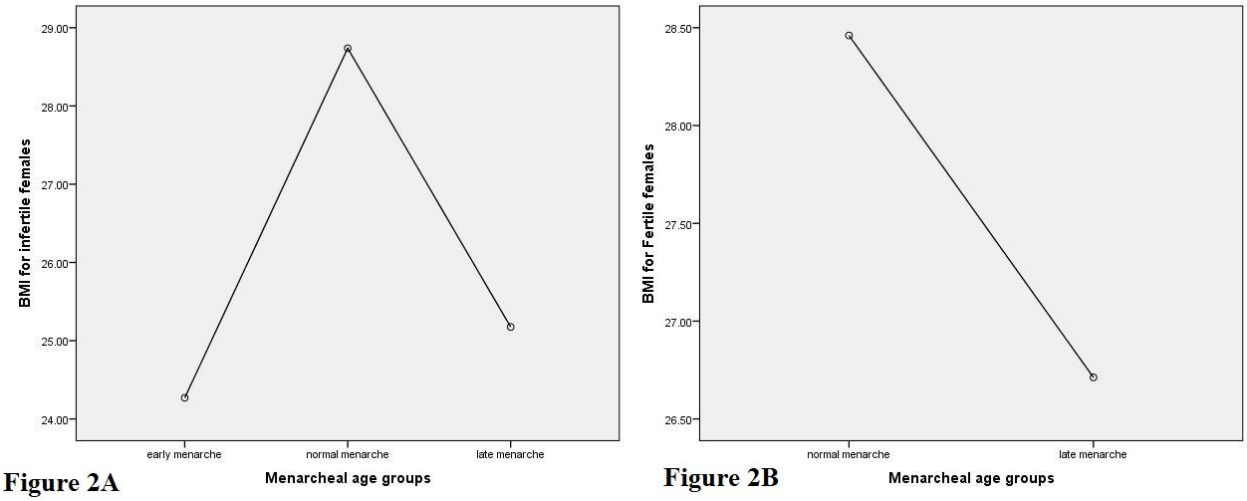

Figure 2: Trend analysis and comparison of BMI between the menarcheal age groups of study participants. **2A**: fertile women; **2B**: women with primary infertility. The mean values of BMI were presented. Values were considered significant at $p<0.05$. BMI: body mass index.

ovarian factor infertility ($\chi2=13.839$, $\varphi_c= 0.458$, $p=0.008$) and tubal factor infertility ($\chi2=11.111$; $\varphi_c=0.527$, $p=0.025$). Table 5 shows the distribution of the clinical diagnosis of infertility across different age categories. There was a high prevalence of cervical factor (16.7%) infertility in women between 20 and 24 years. Cervical factor infertility was the most prevalent (66.7%) cause of infertility in women in the 35-39 year age group, while unexplained infertility was more prevalent within the 30-34 (27.3%) and 40-44 (36.4%) year age category. There was no significant association between the participants' age and any primary female infertility clinical diagnoses ($p>0.05$).

Table 3: Correlation between menarcheal age, BMI and primary infertility duration

Parameters	Test statistic	Menarcheal age in primary infertile female (years)	Menarcheal age in fertile females (years)
BMI (Kg/m^2)	Pearson Correlation	-.067	-.124
	p-value	.629	.392
Infertility duration (years)	Pearson Correlation	-.157	NA
	p-value	.281	NA

BMI = body mass index. In the correlation of infertility duration vs menarcheal age, the sample size is 49 while it is 54 and 50 respectively for cases and controls in the correlation of BMI vs menarcheal age. NA = Not applicable.

Table 4: Association between clinical diagnosis of primary infertility, BMI and menarcheal age

Clinical diagnosis	BMI category, n=54 (χ2 , p-value)	Menarcheal age, n=54 (χ2 , p-value)	Age category, n=54 (χ2 , p-value)
Ovarian disorder (n=33)	17.945, 0.056	13.839, **0.008**	7.071, 0.529
Tubal disorders (n=20)	8.194, 0.610	11.111, **0.025**	8.730, 0.189
Cervical disorders (n=19)	11.098, 0.085	6.401, 0.171	12.339, 0.137
Uterine disorders (n=23)	9.051, 0.338	8.998, 0.061	6.557, 0.364
Hormonal disorders (n=26)	6.500, 0.772	7.800, 0.099	11.237, 0.189
Unexplained factors (n=19)	13.281, 0.208	4.579, 0.333	11.561, 0.172

n=sample size; BMI = body mass index

Table 5: Distribution and relationship between clinical diagnosis of infertility and study age groups

Clinical diagnosis	20-24 years Frequency	25-29 years Frequency	30-34 years Frequency	35-39 years Frequency	40-44 years Frequency	p-value, χ2
Ovarian disorder (n=33)	4.5 (1)	45.5 (10)	13.6 (3)	13.6 (3)	22.7 (5)	7.071, 0.529
Tubal disorders (n=20)	0 (0)	11.1 (1)	22.2 (2)	55.6 (5)	11.1 (1)	8.730, 0.189
Cervical disorders (n=19)	16.7 (1)	0 (0)	0 (0)	66.7 (4)	16.7 (1)	12.339, 0.137
Uterine disorders (n=23)	0 (0)	41.7 (5)	8.3 (1)	25.0 (3)	25.0 (3)	6.557, 0.364
Hormonal disorders (n=26)	0 (0)	43.8 (7)	18.8 (3)	12.5 (2)	25.0 (4)	11.237, 0.189
Unexplained factors (n=19)	0 (0)	18.2 (2)	27.3 (3)	18.2 (2)	36.4 (4)	11.561, 0.172

Data was expressed as percentages and counts (in brackets).

Discussion

Causes and clinical diagnosis of primary infertility

We assessed the causes of primary infertility in the women recruited for this study using their clinical diagnosis of infertility (Tables 2, 4, and 5). Each clinical diagnosis is exclusive of the other, and each participant had the opportunity of declaring more than one clinical diagnosis. Ovarian disorders were the most prevalent diagnosis amongst the study participants, with more than half (67%) of the women declaring the clinical diagnosis (Table 2). This was closely followed by hormonal, uterine, unexplained, and tubal disorders. More than half of the study population is diagnosed with one or more of these disorder classes except for tubal disorder diagnosed in 45% of the infertile women. Our finding is similar to a two-center Nigerian study by Menuba and coworkers[19], which had ovarian factors as a more prevalent cause of infertility. However, it differs from other studies in Nigeria that identified tubal factors[20-26] to be the most prevalent causes of infertility, even though these studies show a combination of secondary and primary infertile patients. Another study found hormonal factors to be more prevalent amongst a population of primary and secondary infertile women[27]. The majority of the previous studies in

the Nigerian population[23-26] showed cervical factors to be the least prevalent, corroborating the finding from our study.

It is important to note the high prevalence of idiopathic female infertility (58%) in this present study. This could be attributed to a combination of factors that include poor diagnosis or misdiagnosis occasioned by the lack of state-of-the-art facilities needed for proper diagnosis or non-access to advanced investigations due to cost[28,29]. Our reports were based on the declarations made by the study participants and as such, may be impacted by the level of knowledge of each patient on their infertility diagnosis. Some tubal, uterine, cervical, and ovarian disorders equally present with endocrine disorders[30] thus may influence the high prevalence observed in the hormonal disorders reported in this study. Our study did not consider causes due to a combination of multiple factors of female infertility. There is a substantial variation in the reports from studies in Nigeria regarding the prevalence of causes of infertility depending on the location, patient characteristics, study design and sample size[31].

It is important to note that the distribution of the clinical causes of primary infertility in our study population did not follow the same pattern as the age distribution (Table 6). We observed varying levels of prevalence of fertility factors across age groups. There was a high prevalence of cervical factor infertility in women between 20-24 years. This age group falls within the 'juvenile age' – the period of increased sexual awareness and exploration, and may explain the anticipated high exposure to sexual activities by this age group, which may contribute to cervical disorders[32]. Cervical factor infertility was the most prevalent cause of primary infertility in women in the 35-39 year age group in this present study, similar to another Nigerian study[23]. Tubal, ovarian, hormonal, and uterine disorders were spread across all age groups, almost similar to age distribution. Unexplained infertility was the most prevalent in the terminal reproductive age group (40-44 years). It could be explained that the treatment of unexplained infertility gives poorer outcomes than other forms of infertility, thus increasing infertility duration in affected individuals[33]. For example, the woman with the highest infertility duration - 20 years - was diagnosed with unexplained primary infertility (data not shown).

Following a proper infertility diagnosis, including molecular investigations, unexplained infertility contributes more to genetic factor infertility[33]. Nigeria still lacks the adequate diagnostic infrastructure (including skills infrastructure) for the genetic diagnosis of primary infertility. This will uncover and inform the treatment of several genetic-based infertility, usually masked as idiopathic infertility[29]. Despite the age variation of the clinical diagnosis of primary infertility, there was no association between any of the clinical causes of primary infertility and the age categories (Table 5). However, there was a strong relationship between ovarian factor infertility ($\chi 2$=13.839, φ_c= 0.458, p=0.008), tubal factor infertility ($\chi 2$=11.111; φ_c=0.527, p=0.025) and the Menarcheal age (Table 5). This finding corroborates previous association studies on Menarcheal age and infertility[12,34-39]. From our data, tubal factor infertility has equal chances of presenting with either normal or late menarche, while ovarian factor infertility presents more with normal menarche. This finding is important for fertility awareness, especially during the adolescent period and during the reproductive age, as a valuable tool in helping women identify gynecological disorders early[40]. It is necessary to critically investigate the mechanism behind the impact of menarche on infertility in order to inform how to improve fertility or prevent primary infertility in females.

The sociodemographic and anthropometric pattern in primary infertility

In this present study, we assessed fifty-four (54) females with primary infertility between 20-44 years in comparison to fertile women to characterise primary female infertility in Nigeria. Hence the primarily infertile females will be the focus of this discussion. The study participants were of a mixed population across religion, ethnicity, and marital status, with the majority being married, establishing the metropolitan, urban nature, and diversity of the study area – Ibadan - predominated by Christians and Yorubas (Table 1)[41]. A long-established finding in a low-prevalence primary infertility study showed that divorced women have significantly higher odds of primary infertility than first-married women[42]. However, from our study, only one infertile female was reported to be divorced during the consecutive

random recruitment compared to none in the fertile group of females, which was not statistically significant (Table 1). This finding questions the generalisation of the effect of divorce on primary fertility.

None of our study participants has less than primary school education, and most are self-employed (Table 1). This demographic data reiterates the typical nature of the study setting - an urban city with high literacy level and a significant number of self employees[43]. It further reveals that the distribution of primary infertility across different categories of a social factor depends mainly on the socio-cultural and economic characteristics of the population. Abnormal BMI has long been associated with female infertility[44,45]. Our study showed an average BMI that indicates an overweight population, as only 35% of the infertile females had a normal weight (Table 1). It is important to understand how exactly BMI plays its role in female infertility. BMI is associated with anovulation, irregular menses, low oocyte quality, and hormonal imbalance[46]. However, our study proved that no difference exists between the average BMI of the infertility cases and control subjects, even in their weight categories. Globally, the prevalence of infertility has been increasing with the increase in overweight and obese patients[47]. Several studies have shown successful outcomes on interventions related to improving fertility through bodyweight loss programs like reduced-calorie diets and exercise, have proved helpful in improving pregnancy rates, live births, and ovulation in infertile women[44,47-49]. Nonetheless, this strategy could be implemented as a supportive treatment model for primary infertility.

History and clinical characteristics of primary infertility

The women who participated in our study reflected a high range of infertility duration (1 -20 years) (Table 2) which underscores low access to assisted reproduction technology (ART) in Nigeria[50,51]. However, our study cohort's median infertility duration was five years, similar to previous studies in Nigeria[19,27]. This is an indication that our study population could attain pregnancy following treatment, as infertility duration less or equal to five years is associated with higher pregnancy[19]. There was no significant difference in the average menarcheal age of the fertile and infertile females from this present study. The study average indicates a normal menarcheal age in both populations even though the fertile females had a lesser menarcheal age than the infertile females (Table 2). A few of the participants belong to the abnormal menarcheal classification in both fertile and infertile groups. This outcome corroborates the study by Adamson and colleagues[52]. In their study, even though there was a significant difference between the average menarcheal age of primarily infertile and fertile women - with fertile women having a lower value - both group averages were still normal. Our study agrees with other studies in the Nigerian population on menarcheal age[53,54]. A multi-country population study has reported that fertility and adult female mortality rates correlates positively with menarche, indicating that both high fertility and high mortality are associated with a late menarche[12]. Thus, Nigerian female population is expected to have a higher menarcheal age average, being in the high mortality and fertility rate country category[12]. However, our study showed only a significant correlation between menarcheal age and infertility amongst the tubal and ovarian factor infertility subgroup (Table 4). This present study did not determine the mechanism involved in the observed relationship between menarcheal age and infertility. The trend analysis showed an increased infertility duration in females with early and late menarche (Figure 1), with homogenous variances between the menarche groups. Also, the trend analysis revealed an increased BMI in females with normal menarche and lowered BMI in late menarche across fertile and infertile females. Howbeit, these observations were not significant. Howbeit, we found no significant correlation between the menarcheal age, BMI, and primary infertility duration (Table 3). This observation is different from a study in the Saudi population that reported a significant negative correlation between BMI and menarcheal age[55]. In their study, the dissimilarity in the menarcheal grouping and the sample size between their study and the present study may have caused the difference in their study outcome compared to this present study. We have accessed the occupation of our study participants to understand the relationship it has with their fertility status. Compared to other occupation, well-trained athletes or dancers[56,57] usually have a higher prevalence of primary amenorrhea. Our study had a slight chance

of recruiting people who engage in athletic occupation (Table 1), unless for women with multiple jobs, who were restricted by the proforma to report all their occupation during the interview. This explains the normality of the menarcheal age observed in this present study, as it was likely not influenced by the women's occupation. Other studies have earlier shown that abnormal menarcheal age (early and late menarche) reduces the female reproductive ability and serves as a risk factor for primary infertility[12,34,35]. We recorded a zero prevalence for smoking amongst our study participants. Only a few women reported having taken alcohol for less than one year or between 1- 5 years, which does not vary significantly in the cases and control subjects (Table 2). Past studies have found smoking to impact fertility in the general population[58-60]. However, clinical studies suggest that smoking is associated with decreased fertility and may increase the risk of pregnancy loss among couples undergoing infertility treatment[61]. Generally, smoking by females has opposing effects on outcomes of infertility treatment with ART[61,62]. The low prevalence of smoking in South-west Nigeria[63] could be responsible for the zero prevalence of smoking in our study cohort. Studies addressing the effect of alcohol consumption on female fertility provide conflicting results, although the majority reported a lack of a correlation between alcohol consumption and female fertility[64-69]. Our data show a significantly low prevalence (9%) of prior or current use of contraceptives by infertile females compared to fertile females (38%). The use of modern contraceptives has been increasing over the years, which explains the significantly higher prevalence in fertile females. However, the prevalence in infertile females differs from the 15% national prevalence rate[70-72]. Concerns about future fertility (before marriage) or current fertility status may have influenced this lifestyle choice of infertile women[73]. However, studies have shown that contraceptive use, regardless of type and duration, does not negatively affect the ability of women to conceive following disuse, and does not significantly delay fertility[74-76]. Expert opinions have posited that family history may be playing an insignificant role in a woman's ability to conceive. However, some reproductive disorders can be inherited from mother to child and may predispose one to infertility[7]. Reproductive disorders and risk factors of infertility like Polycystic Ovarian Syndrome (PCOS), endometriosis, uterine fibroids, Fragile X, and Down syndrome are associated with either inheritance of similar disease or reproductive decline in the offspring[7]. Our study shows that only seven infertile women (13%) had a family history of infertility (Table 2). It is important to note that 6 out of 7 and 3 out of 7 of these women reported infertility diagnoses for their sisters or mothers, respectively, compared to fertile women who reported only 4 out of 14 and 2 out of 14. Albeit, there is no statistical significance observed in these variations. There is a need for a critical look into the heritability of female infertility across different models of infertility and population.

There was a low prevalence of diabetes and hypertension in our study cohorts and without any significant variation (Table 2). Women with type 1 diabetes have reduced fertility, though this has normalised in the past 20 years in women with uncomplicated disease[77]. PCOS is primarily associated with type 2 diabetes[78], and many women with diabetes experience irregular periods, premature menopause, and endometrial cancer[79]. Recently, it was reported that abnormal preconception blood pressure levels were associated with prolonged time to pregnancy among couples who were attempting to conceive their first pregnancy. However, this staggering claim needs to be further validated[80].

Only one person each reported the history of having been diagnosed with either HSV, HIV, Syphilis, TB, or Hepatitis amongst the infertile females assessed in this study. Also, only two women reported having been infected or currently infected with Chlamydia (Table 2). Only HIV was the only infectious disease reported to have been experienced by the fertile female participants. None of our study participants reported Human papillomavirus (HPV) and Gonorrhea infections. Using clinical proforma instead of standard laboratory test evidence to assess the current state or past diagnosis of these infections may have affected the study outcome. The emerging impact of infectious diseases on female infertility still looks indistinct and unexplored. However, some preliminary evidence exists. The effects of HIV infection on fertility have been extensively studied in generalised HIV epidemic settings in sub-Saharan Africa[81-86]. The fertility rate ratio (FRR) among HIV-positive women becomes increasingly lower relative to HIV-negative women[86,87]. HSV-2

seropositivity with 19.5 % prevalence was significantly associated with primary infertility in infertile women[52]. Cherpes *and colleagues*[88] have also demonstrated an association and mechanism behind the role of HSV-2 infection in female infertility. Their study showed that HSV-2 infection might cause lower-genital tract ulcerations and host inflammatory responses in the upper genital tract, leading to Pelvic inflammatory disease (PID) or tubal damage, respectively. Suppose sexually transmitted infections like Syphilis, Gonorrhea, Chlamydia, and HPV are not treated in women of reproductive age; they could be predisposed to some reproductive malfunctions such as PID, miscarriage, stillbirth, and even reproductive cancers[89]. Hepatitis B (HBV) infection is associated with tubal infertility in women of reproductive age by increasing the risk of pelvic infection through impaired immune response to sexually transmitted infections[90]. Infertile Women with HBV usually present with increased infertility duration, ovulatory disorders, and lower implantation rate than fertile women; However, HBV infection status does not affect the clinical pregnancy, miscarriage, or live-birth rates[91].

Pulmonary TB is the primary manifestation of TB, but genital TB is also found in many women[92]. In this current study, our assessment of TB status did not specify the type of TB, just like Hepatitis. There have been reports detailing an increase in TB cases presenting to gynecological clinics, partly due to a growing population and partly due to an overall global rise in infertile patients with TB[93]. Female genital TB is concomitantly present in 10% of all pulmonary TB cases and accounts for 5% of all female pelvic infections[94-95]. Genital TB may be found in high-risk groups, such as those with infertility, recurrent miscarriages, ectopic pregnancies, adnexal mass, chronic pelvic pain, family history of TB, history of previous TB and menstrual irregularities (including menorrhagia, oligomenorrhea, and amenorrhea)[96]. The fallopian tubes are the likely site of initial infection in the majority of the cases, and bilateral involvement of the fallopian tubes is common[95,97,98]. The low prevalence of infectious diseases witnessed in this present study could be as a result of the relatively low sample size of our study compared to studies with other studies with a higher prevalence. This present study could not ascertain any difference in the prevalence level of the infectious disease in the fertile and infertile groups as there was zero prevalence in almost all the infectious diseases assessed in fertile females, hindering statistical comparison. There is a need to critically evaluate the role of infectious diseases in female infertility using a larger cohort to delineate the indistinct pieces of evidence currently available.

Limitations

This study presented a useful characterisation of primary female infertility in a Nigerian setting. However, its outcomes and arguments were based on relatively small sample size and within a single clinical setting. This may have added some subjectivity bias to its evidence. Hence, some of its conclusion may not be generalisable to other settings. We were constrained with the objectives of the major study from which this study emanated, and as such, some clinical details of the primary infertile patients were not captured. The data used for this study were obtained through patient-reported interviews, and some responses appear to be retrospective in nature; thus, the participants' responses could not be validated. However, efforts were made as much as possible to validate the information reported by participants through the patient records especially for the participants who are not first-time visitors of the study recruitment clinics.

Ethical approval and consent to participate

The study protocol was reviewed and approved by the University of Ibadan/University College Hospital (UI/UCH) Ethics Committee (Assigned number: UI/EC/20/0220; Registration Number: NHREC/05/01/2008a) (supplementary file 2). A consent form was administered to all study participants (supplementary file 3). A signature or thumbprint of the participant was appended at the end of the form before being enrolled in the study. All the study participants retained a copy of the information sheet. All the necessary information regarding the study (objectives, requirements for participation and duration of the study) were made available to all prospective study participants on an information sheet in English (translated verbally to native language when needed) to ensure an informed decision to participate in the study.

Ethical views such as discretion/confidentiality, free consent of the interviewees as well as beneficence and non-maleficence to participants were scrupulously respected.

Conclusions

Primary female infertility remains a serious reproductive health concern in Nigeria. It is responsible for a longer duration of infertility amongst females, and the causes of primary infertility remain unchanged across different age groups. Either normal or abnormal menarcheal age could precede primary female infertility. However, menarcheal age shows a significant association with tubal and ovarian factor infertility. Also, the presence of diabetes, hypertension, infectious diseases, alcohol consumption and smoking are not distinguishing features of women with primary infertility. Ovarian factor infertility appears to be re-emerging in the studied population while unexplained infertility remains much prevalent in Nigeria, and demands that more advanced diagnoses be employed in infertility management to delineate and treat the specific infertility causes. The reproductive healthcare experts must pay attention to the changing landscape of primary infertility and ensure to use a holistic approach for fertility assessment and management.

Competing interests

The authors have no conflict of interest to declare.

Authors' contributions

IAO, OO, and AOO conceived and designed the study. IAO and OOS recruited the study participants and performed the initial assessment of data. IAO performed the data analysis and wrote the first draft. OOS, OO, and AOO reviewed the manuscript draft. All the authors read and approved the final manuscript draft.

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